UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/887,854	06/21/2001	Krys Bankiewicz	0800-0014.01	9216

31048 7590 01/30/2003

COOLEY GODWARD LLP (R & P)
FIVE PALO ALTO SQUARE
3000 EL CAMINO REAL
PALO ALTO, CA 94306-2155

EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/30/2003 (10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/887,854	Bankiewicz et al.
Examiner	**Art Unit**
Shin-Lin Chen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *6-21-01 and 9-4-01*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *21-25* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *21-25* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 6
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' preliminary amendments filed 9-4-01 and 7-8-02 have been entered. Claims 1-20 have been canceled. Claims 21-25 have been added. Claims 21-25 are pending and under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 21-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "rAAV" in claims 21, 22 and 25 is vague and renders the claims indefinite. The term "rAAV" is an abbreviation that can have different meanings. The metes and bounds of the term "rAAV" is unclear. Spelling out the term "rAAV" would be remedial. Claims 23 and 24 depend on claim 22 but fail to clarify the indefiniteness.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 21-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for delivering recombinant adeno-associated virus (rAAV) expressing aromatic amino acid decarboxylase (AADC) to monkey brain by intrastriatal administration of said rAAV via convection enhanced delivery, expression of AADC in striatum and conversion of L-dopa to dopamine in said striatum of monkey brain, does not reasonably provide enablement for a method of delivering a pharmaceutical composition comprising a rAAV expressing any therapeutic protein to the brain of a subject having central nervous system (CNS) disorder and the expression of said therapeutic protein provide a therapeutic effect for various CNS disorders in said subject via various administration routes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 21-25 are directed to a method of delivering a pharmaceutical composition comprising a rAAV expressing a therapeutic protein to the brain of a subject and the expression of said therapeutic protein provide a therapeutic effect in said subject. Claims 22-24 specify the rAAV is delivered using convection enhanced delivery (CED), such as infusion pump and osmotic pump.

The specification only discloses delivering recombinant adeno-associated virus (rAAV) expressing aromatic amino acid decarboxylase (AADC) to a monkey brain by intrastriatal administration of said rAAV via convection enhanced delivery, expression of AADC in striatum and conversion of L-dopa to dopamine in said striatum of monkey brain. The claims encompass

using a pharmaceutical composition comprising a rAAV expressing any therapeutic protein to the brain of a subject to provide therapeutic effect for various CNS disorders, such as migraine, Parkinson"s disease, Alzheimer's disease, glioma, neuroblastoma, multiple sclerosis, schizophrenia etc., in a subject via various administration routes in addition to CED.

The phrase "pharmaceutical composition" implies therapeutic effects *in vivo* and the claims also recite providing therapeutic effect in the subject. Thus, the claims read on gene therapy *in vivo*, and the scope of the claims is very broad and encompasses numerous CNS disorders, including migraine, Parkinson"s disease, Alzheimer's disease, glioma, neuroblastoma, multiple sclerosis, Huntington's disease, spinal cerebellar ataxia, schizophrenia etc. The specification fails to provide correlation between a therapeutic protein and a particular CNS disorder such that expression of said therapeutic protein could provide therapeutic effect for said particular CNS disorder *in vivo*. Absent such correlation, one skilled in the art at the time of the invention would not know which gene expressing a therapeutic protein should be used for what CNS disorder.

The specification also fails to provide adequate guidance and evidence for how to deliver a pharmaceutical composition comprising a rAAV expressing any therapeutic protein to the brain of a subject such that expression of said therapeutic protein would provide therapeutic effect for various CNS disorders in a subject via various administration routes including CED.

The state of the art for gene therapy was unpredictable at the time of the invention. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired

tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82).

In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract). In view of the reasons set forth above, one skilled in the art at the time of the invention would not know how to use a rAAV expressing various therapeutic proteins to the brain of a subject such that expression

of said therapeutic proteins could provide therapeutic effects for various CNS disorders in a subject via various administration routes.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the absence of working examples and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claim 21 is rejected under 35 U.S.C. 102(a) as being anticipated by Mizuno et al., January 1998 (Jpn. J. Cancer Res., Vol. 89, p. 76-80).

Claim 21 is directed to a method of delivering a pharmaceutical composition comprising a rAAV expressing a therapeutic protein to the brain of a subject and the expression of said therapeutic protein provide a therapeutic effect in said subject.

Mizuno teaches delivering AAV vector expressing a herpes simplex virus thymidine kinase (HSV-tk) gene to a human glioma transplanted into the brain of nude mice followed by intraperitoneal injection of GCV and observed complete regression of the tumors and the survival of mice treated with AAV-tk vector and GCV were markedly prolonged (e.g. abstract). Thus, claim 21 is anticipated by Mizuno.

7. Claims 21 and 25 are rejected under 35 U.S.C. 102(a) as being anticipated by Leff et al., 1997 (Society of Neuroscience Abstracts, Vol. 23, No. 1-2, pp 541).

Claims 21 and 25 is directed to a method of delivering a pharmaceutical composition comprising a rAAV expressing a therapeutic protein to the striatum of brain of a subject and the expression of said therapeutic protein provide a therapeutic effect in said subject.

Leff teaches that intrastriatal injection of rAAV vector encoding human AADC in 6-OHDA lesioned rats restores AADC activity to control level and reports significant difference of dopamine level in the rAAV-hADDC injected rats after administration of L-dopa. Thus, claims 21 and 25 are anticipated by Leff.

8. Claim 21 is rejected under 35 U.S.C. 102(b) as being anticipated by Okada et al., 1996 (Gene Therapy, Vol. 3, p. 957-964).

Claim 21 is directed to a method of delivering a pharmaceutical composition comprising a rAAV expressing a therapeutic protein to the brain of a subject and the expression of said therapeutic protein provide a therapeutic effect in said subject.

Okada teaches stereotactic delivery of AAV-tk-IRES-IL2 particles into the tumor in the brain of nude mice followed by administration of GCV and reports 35 fold reduction in the mean volume of the tumors as compared to controls (e.g., abstract). Thus, claim 21 is anticipated by Okada.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 21-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Okada et al., 1996 (Gene Therapy, Vol. 3, p. 957-964) in view of John, P., 1995 (WO 95/34670) and Zhu et al., 1996 (Gene Therapy, Vol. 3, No. 6, p. 472-476).

Claims 21-24 are directed to a method of delivering a pharmaceutical composition comprising a rAAV expressing a therapeutic protein to the brain of a subject suffering CNS disorder and the expression of said therapeutic protein provide a therapeutic effect in said subject. Claims 22-24 specify the rAAV is delivered using convection enhanced delivery (CED), such as infusion pump and osmotic pump.

Okada teaches stereotactic delivery of AAV-tk-IRES-IL2 particles into the tumor in the brain of nude mice followed by administration of GCV and reports 35 fold reduction in the mean volume of the tumors as compared to controls (e,g, abstract).

Okada does not teach using infusion pump or osmotic pump to deliver the rAAV vector to the brain of a subject suffering various types of CNS disorder.

Johnson teaches a method for treating a neurodegenerative disorder, such as Alzheimer's disease, cancer, Parkinson's disease and Huntington's disease, comprising administering a therapeutically effective dose of a recombinant AAV encoding an AADC, nerve growth factor, NT-3, or tyrosine hydroxylase etc., to a host exhibiting said neurological disorder (e.g. p. 8, 36, 39).

Zhu teaches using a minipump combined with stereotaxic techniques to continuously deliver therapeutic genetic materials into the brain and reports that continuous intracerebral

delivery of HSVtk gene-liposome complex into the brain via an osmotic minipump results in complete tumor regression in 36.4% of the treated animal (e.g. abstract).

It would have been obvious for one of ordinary skill at the time of the invention to deliver the AAV-tk-IRES-IL2 particles to the brain as taught by Okada via the use of osmotic minipump as taught by Zhu because they both teach delivering DNA encoding therapeutic protein, i.e. HSV-tk, into the brain of an animal to inhibit tumor growth and osmotic minipump is an administration technique for gene delivery, thus, it would have been obvious for one of ordinary skill to use osmotic pump for AAV vector delivery.

One having ordinary skill at the time the invention was made would have been motivated to do so in order to deliver AAV vector encoding a therapeutic protein to the brain of an animal to inhibit glioma tumor growth as taught by Okada or to treat various neurodegenerative disorder as taught by Johnson with reasonable expectation of success.

It should be noted that only abstract of the cited reference Zhu et al., 1996 (Gene Therapy, Vol. 3, No. 6, p. 472-476) is attached to this Official action. Full-length article of Zhu will be provided in the Official action that follows.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.